Chapter 2

BLOOD CARBOXYHEMOGLOBIN LEVELS OF CIGARETTE SMOKERS AND NONSMOKERS

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Prior to the discussion of the possible health hazards of carbon monoxide contained in cigarette smoke, it is necessary to review the levels of carboxy-hemoglobin in the blood of smokers. Measurements show a striking variability depending on the following: (a) the nature of the cigarette (presence of filter, porosity of the paper and type of tobacco); (b) frequency and depth of inhalation of the smoker; and (c) the carbon monoxide level in the immediate environment of the smoker. The last-mentioned factor represents the load or basic level of carbon monoxide in the ambient air that all persons are exposed to, smokers and otherwise. The overall exposure to occupational, residential and vehicular sources of carbon monoxide varies geographically.

It is possible to measure the amount of carbon monoxide in the ambient air and calculate the time-weighted levels of exposure in the course of a day. However, the quantitative expression of carboxyhemoglobin level in the blood is usually based on the analysis of a single sample. The carboxyhemoglobin level of a smoker fluctuates so much during the day that it is erroneous to regard the results of a single blood analysis as representative of a 24-hour level of carboxyhemoglobin. There is a transient elevation of carboxyhemoglobin immediately after smoking a cigarette but there is also a reduction during the nonsmoking interval. The rate of excretion of carbon monoxide is dependent on the physical activity of the smoker, another variable influencing carboxy-hemoglobin level. The techniques for recording carboxyhemoglobin levels are

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more complex than that for carbon monoxide in the ambient air. Unless there is an improvement in technology, it is unlikely that a time-weighted value for carboxyhemoglobin in the blood of smokers will become available.

Almost all investigators use single measurements of carboxyhemoglobin as an approximation of the amount of carbon monoxide absorbed by cigarette smokers. Since the level is higher than that of nonsmokers, they conclude that the difference is due to the cigarette smoke. The inaccuracy in the comparison of carboxyhemoglobin levels of smokers and nonsmokers is discussed in this chapter.

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A. Carboxyhemoglobin Levels of Blood Donors

Blood donors have been used to compare the carboxyhemoglobin levels of smokers and nonsmokers. There is general agreement that the comparisons show higher levels of carboxyhemoglobin in smokers than in nonsmokers. However, it should be recognized that blood donors are selected individuals, some of them are professionals who derive part of their income in exchange for blood. The socioeconomic status of donors is different from those who do not engage in such an activity.

1. National Survey Conducted by Stewart et al.

From 1969 to 1972, Stewart and his collaborators conducted a survey of American blood donors for the purpose of determining the range of carboxyhemoglobin levels. Venous blood samples were obtained from 29,000 blood donors living in urban, suburban and rural communities in 18 metropolitan areas.[1-3] The carboxyhemoglobin saturation of blood donors in the various cities are tabulated on the next page.

The median carboxyhemoglobin saturation for the smokers is higher than that of nonsmokers. The magnitude of the differences between medians varies from city to city; the smallest difference is 2.0 (% saturation) for Houston; the largest is 4.4 for Los Angeles. It is unlikely that smokers smoke less in Houston than in Los Angeles. The difference in median levels for these cities reflects differences in the magnitude of exogenous sources of carbon monoxide.

a. Significance of carboxyhemoglobin levels of nonsmokers. Stewart et al.[1-3] noted that 45% of all the nonsmoking blood donors tested had carboxyhemoglobin saturations of more than 1.5%. This conclusion has been challenged by other investigators[4,5] who question the accuracy of the technique used by Stewart et al.[6]

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for the measurement of carboxyhemoglobin. The absolute values of carboxyhemoglobin levels are questionable. Even though the technique is accepted, the levels demonstrate the combined amount of endogenous (formed in the body) and exogenous sources of carbon monoxide (from cigarette smoking, vehicular emissions and occupational exposure).

Location	Median and 90% range of carboxyhemoglobin saturation		
	Cigarette Smokers	Nonsmokers	Δ Median
Anchorage	4.7 (0.9-9.5)	1.5 (0.6-3.2)	3.2
Chicago	5.8 (2.0-9.9)	1.7 (1.0-3.2)	4.1
Denver	5.5 (2.0-9.8)	2.0 (0.9-3.7)	3.5
Detroit	5.6 (1.6-10.4)	1.6 (0.7-2.7)	4.0
Honolulu	4.9 (1.6-9.0)	1.4 (0.7-2.5)	3.5
Houston	3.2 (1.0-7.8)	1.2 (0.6-3.5)	2.0
Los Angeles	6.2 (2.0-10.3)	1.8 (1.0-3.0)	4.4
Miami	5.0 (1.2-9.7)	1.2 (0.4-3.0)	3.8
Milwaukee	4.2 (1.0-8.9)	1.2 (0.5-2.5)	3.0
New Orleans	5.5 (2.0-9.6)	1.6 (1.0-3.0)	3.9
New York	4.8 (1.2-9.1)	1.2 (0.6-2.5)	3.6
Phoenix	4.1 (0.9-8.7)	1.2 (0.5-2.5)	2.9
St. Louis	5.1 (1.7-9.2)	1.4 (0.9-2.1)	3.7
Salt Lake City	5.1 (1.5-9.5)	1.2 (0.6-2.5)	3.7
San Francisco	5.4 (1.6-9-8)	1.5 (0.8-2.7)	3.9
Seattle	5.7 (1.7-9.6)	1.5 (0.8-2.7)	4.2
Vermont, New Hampshire	4.8 (1.4-9.0)	1.2 (0.8-2.1)	3.6
Washington, DC	4.9 (1.2-8.4)	1.2 (0.6-2.5)	3.7

b. Significance of carboxyhemoglobin levels of smokers. Stewart et al.[1-3] reported that the median for carboxyhemoglobin saturation for smokers ranged

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from 3.2 to 6.2%. These investigators also observed that the carboxyhemoglobin levels were influenced by the quantity of tobacco used in the previous 24 hours as well as by the time elapsed since the last cigarette smoked. One hour after the last cigarette, the mean values for carboxyehmoglobin saturation in cigarette smokers were as follows:

Location	Non-smoker	Smoker: packs of cigarettes smoked per day				
		<1/2	1/2-1	1	1 1/2	2
Milwaukee	1.3	3.0	4.2	5.3	6.2	4.7
New Hampshire and Vermont	1.4	3.3	4.4	5.7	6.7	5.3
New York City	1.4	3.1	4.3	4.7	5.8	6.3
Washington, DC	1.4	3.8	4.6	5.2	5.8	6.6
Los Angeles	2.0	4.0	5.2	6.0	7.4	7.5
Chicago	2.0	4.8	5.4	6.3	7.1	7.7

The above numbers are quoted from the original article by Stewart et al.[1] There are no reported Ranges or Standard Deviation to evaluate the results for statistical significance. The groups of smokers from Milwaukee do not show a dose-response curve; the mean carboxyhemoglobin saturation for smokers of 1 1/2 packs per day was higher than those consuming 2 packs per day. The 2-pack smokers from New Hampshire and Vermont have lower mean saturation than the 1-1/2 pack smokers. Smokers in urban areas such as New York City and Washington have mean saturation levels about the same as smokers in rural states (New Hampshire and Vermont). These values conflict with what has been reported by other investigators. The conclusions of this study apply only to the selected group of blood donors and not to the general population of smokers and nonsmokers.

c. Significance of difference between smokers and nonsmokers. Stewart

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et al.[1] recognized that carboxyhemoglobin saturation can be influenced not only by geographical location of the individual, but also by the existing meteorological conditions and the occupation of the individuals. It has not been possible to match the occupational and environmental factors for the smokers and nonsmokers for each metropolitan area so that the difference in blood levels cannot be ascribed to smoking alone. The contributions of vehicular traffic and occupational sources of carbon monoxide to blood carboxyhemoglobin levels are discussed elsewhere (Chapters 6 and 7).

2. Metropolitan St. Louis Survey by Kahn, Wallace and Collaborators.

Blood samples from blood donors in the St. Louis area were collected for a 12-month period in 1971 and 1972. Kahn, Wallace and their collaborators reported the mean carboxyhemoglobin saturation for 16,649 donors. The mean and standard errors were as follows:

	COHb % Saturation
Total sample (16,649)	2.30 ± 0.02
Nonsmokers (10,157)	0.85 ± 0.01
Smokers (6,492)	4.58 ± 0.03

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The levels reported above are different from those observed by Stewart et al.[1-3] for 500 blood donors from St. Louis (see above). The median values were 1.4 for nonsmokers, and 5.1 for smokers. It is on this basis that Kahn et al.[4] questioned the accuracy of the technique used by Stewart et al.[6] who overestimated the carboxyhemoglobin levels in the blood samples.

Kahn et al.[7-11] have identified several factors that correlated with the carboxyhemoglobin levels. They are as follows: occupational exposure, socioeconomic data, travel time or distance, racial difference and ambient carbon monoxide levels.

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Although the carboxyhemoglobin levels of smokers were higher than nonsmokers, the difference is not caused by smoking alone. Kahn et al.[8] reported data indicating that industrial occupation and the type of tobacco smoked influence the carboxyhemoglobin levels. There are also differences between sexes; when men and women smoke at the same rate and reach the same equilibrium level of carboxyhemoglobin, women achieve lower levels after ceasing smoking for the day. Physiological differences such as blood volume, hemoglobin, pulmonary vital capacity and carboxyhemoglobin excretion, in addition to varying ambient exposures associated with travel and employment were suggested as explanations for the differences in male and female post-smoking carboxyhemoglobin values.

3. Survey in Israel by Torbati et al.

A group of 500 male Israeli blood donors were examined by Torbati et al.[12] The mean and Standard Deviation of carboxyhemoglobin saturation are as follows:

nonsmokers (231 subjects)	0.70 ± 0.71
smokers (269 subjects)	3.43 ± 1.69

In addition to the above results, there was also a correlation noted between blood levels and occupational exposure to carbon monoxide for both smokers and nonsmokers. These conclusions are essentially similar to those based on American donors (see above).

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4. Interpretation of Carboxyhemoglobin Levels of Blood Donors.

The results of the surveys indicate that carboxyhemoglobin levels of

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smokers are higher than nonsmokers. However, there is no agreement as to a mean or median value for carboxyhemoglobin saturation. For metropolitan St. Louis, the mean for 16,649 donors is 4.58 (see 2 above); for 18 cities, the medians range from 3.2 to 6.2 (see 1 above); and for Israel, the mean is 3.43% saturation (see 3 above). The variability in reported mean or median values is a reflection of the degree of exposure to carbon monoxide in the ambient air which differs in various cities. A single blood analysis does not reflect the mean level during a 24-hour period. The technique used by one group of investigators has been criticized by Radford et al.[5] and by Cole[13] as being capable of errors and inaccurate so that the reported mean and median values may be overestimations of the true carboxyhemoglobin levels of smokers.

It is important to point out that the elevation of carboxyhemoglobin levels in smokers has led to the suggestion that they should not be used to donate blood.[14] On the other hand, it is recognized that the amount of carboxyhemoglobin is small and is diluted by the blood volume of the recipient and that carbon monoxide is ultimately eliminated from the recipient.[15,16] Even more importantly, there is no agreement on the consequence of low levels of carboxyhemoglobin that would be expected from the recipient. There is no evidence that the elevation of carboxyhemoglobin saturation in the donors blood is a hazard to the recipient.

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B. Carboxyhemoglobin Levels in Smokers

The results of analysis of blood samples from donors described in the preceding section represent the most recent attempts to show that smokers are likely to absorb carbon monoxide in the course of inhaling cigarette smoke. From the historical standpoint, it should be recalled that Wahl,[17] in 1899, was the first to demonstrate the presence of carbon monoxide in cigarette smoke and that Hartridge,[18] from 1919 to 1920, was the first to identify carboxyhemoglobin in the blood of smokers. The subsequent developments in this area of investigation are reviewed in this section.

1. Carbon Monoxide Content of Cigarette Smoke.

In the initial investigation by Wahl,[17] the presence of carbon monoxide in tobacco smoke was demonstrated by exposing a few drops of blood to 2 or 3 mouthfuls of tobacco smoke, and detecting carboxyhemoglobin by spectroscopy. A more direct approach has been to measure the amount of carbon monoxide from burning tobacco the results of which are as follows:

Investigators (year)	ml carbon monoxide/g tobacco
Marcelet (1907)[19]	20-80
Lee (1908)[20]	4.1
Lehmann (1909)[21]	15-23.5
Baumberger (1923)[22]	8.3
Ehrismann and Abel (1934)[23]	17.25-35
Saruta (1937)[24]	62.7
Kohn-Abrest (1949)[25]	40.0

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The total amount of carbon monoxide ranged from 4 to 80 ml per g of tobacco.

Subsequent analysis for carbon monoxide has been expressed as percentage contained in the cigarette smoke. The results are as follows:

Investigators (year)	% carbon monoxide
Armstrong (1922)[26]	0.8-1.24
Philippe and Hobbs (1956)[27]	2.8-5.7
Osborne et al. (1957)[28]	3.3-5.7
Mumpower et al. (1962)[29]	5.1
Newsome and Keith (1965)[30]	5-11
Jarrell and Burde (1965)[31]	0.5-1.0
Harke and Drews (1968)[32]	3.4-7.7
Kruszynski and Henriksen (1969)[33]	3.5-8.1
Otsuka et al. (1970)[34]	1.6-5.6
Morie (1973)[35]	4.25-5.35

The above results show a wide range of values among various investigators, because of the differences in collection of smoke and the technique for analysis of carbon monoxide. For the same investigator, there is still a variation in concentration of carbon monoxide depending on the type of tobacco, speed of burning the cigarette, and the amount of air diluting the smoke. Even for the same cigarette, there is an increase of carbon monoxide concentration as the cigarette burns closer to the butt or filter tip.[36-40]

The porosity of the cigarette paper can also influence the concentration of carbon monoxide in the cigarette smoke.[41-43] The nature of the filter also alters the amount of carbon monoxide generated.[44-46] These figures,

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if accurate, are reflective of only the precise conditions of type of tobacco, volume and frequency of the inspired smoke, porosity of the paper and the nature of the filter. A slight variation in any component would change the concentration of carbon monoxide in the cigarette smoke.

2. Amount of Carbon Monoxide Absorbed in the Lungs.

The cigarette smoke in the mainstream, although inhaled in its undiluted form, is immediately mixed by the air in the lungs of the smoker. The first estimation of the amount of carbon monoxide absorbed by cigarette smokers was made by Baumberger in 1923 by comparing the concentration of inhaled smoke and the expired air. In a group of six subjects, about 61% of the carbon monoxide was absorbed.[47] Bokhoven and Niessen reported absorption of 82 to 87% in three subjects,[48] whereas, Dalhamn et al. reported a carbon monoxide retention of 54 ± 12.7% in five subjects.[49] These results refer to the amount of carbon monoxide of the smoke that has been diluted by the alveolar air.

The above results are not surprising because carbon monoxide diffuses readily across the alveolar membrane and combines readily with hemoglobin. However, the above observations were not accompanied by measurements of carboxyhemoglobin saturation in the blood to determine whether the amount absorbed is significant enough to elevate the carboxyhemoglobin saturation. Even if there should be a significant elevation in carboxyhemoglobin, it would be disposed of in the same manner as the carbon monoxide absorbed from the ambient air derived from sources other than cigarette smoke. The rates of disposition of carbon monoxide from various sources have not been examined simultaneously with absorption studies.

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3. Carboxyhemoglobin Levels Associated with Cigarette Smoking.

In the face of varying concentrations of carbon monoxide in the cigarette smoke, the disparate frequency of smoking and the volume of smoke inhaled that is diluted with alveolar air, and a wide range of absorption of carbon monoxide (54 to 87%), it is not surprising to note that the reported levels of carboxyhemoglobin of smokers are as varied. The results, as they relate to the environmental level of carbon monoxide which vary according to the geographical location of the study, are as follows:

City and Investigators	No. of subjects = mean (range) COHb nonsmokers	smokers
Chicago Hanson and Hastings (1933)[50]	7=1.5 (1.2-1.9)	9=2.1 (2.0-6.7)
Boston Gaensler et al. (1957)[51]	9= (0.6-1.2)	10= (3.1-7.8)
Los Angeles Motley (1971)[52]	115=1.5 (0.2-2.9)	81=5.7 (3.2-14.2)
Sunderland, Great Britain Trinder and Harper (1962)[53]	23=0.9 (0.4-2.1)	15=2.6 (0.7-6.5)
Munich, Germany Scheidemandel and Daum (1973)[54]	26=2.4 (1.6-5.0)	19=7.4 (2.8-13.4)
Milan, Italy Parmeggiani and Gilardi (1952)[55]	9=2.8 (0-4.0)	14=4.9 (1-9)
Genova, Italy Kanitz et al. (1973)[56]	164=1.2 (0.2-3.3)	34=2.3 (0.5-6.1)
Tokyo, Japan Muroya and Kubota (1974)[57]	30=0.7 (0-3.3)	28=3.5 (0.9-8.3)
Zagreb, Yugoslavia Valic and Duric (1954)[58]	75=0.9 (0-2.4)	75=3.8 (0-5.7)

The above results show the wide range of values for smokers. In each series of comparisons, the range for smokers is two to seven times the range of nonsmokers value for carboxyehmogolbin levels. The wide range is, in part, caused by the fluctuation of carbon monoxide in the mainstream that is diluted by the inspired

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air in the course of smoking a cigarette. Furthermore, the pattern of frequency and volume of smoking a cigarette, and the total daily consumption varies from smoker to smoker so that it is not surprising that carboxyhemoglobin levels differ widely among smokers.

a. Time-blood carboxyhemoglobin relationships. There are a few studies which include more than one sampling of blood for carboxyhemoglobin analysis.[59-61] The results indicate a rise followed by a fall in carboxyhemoglobin saturation in the course of smoking a cigarette. Ashton and Telford[62] analyzed four to six finger-prick samples in the course of 20 min for each of five smokers. The peak level was reached immediately after consuming one cigarette which was followed by a fall with half recovery to control level in about 5 to 15 min.

Castleden and Cole[63] inserted an indwelling venous cannula in each of six smokers. By repeated analysis of the blood, the carboxyhemoglobin level remained fairly constant throughout 24 hours, and there was no rise at the end of the day. That each smoker maintains his carboxyhemoglobin level challenges the theory of Goldsmith et al.[64-66] and others[8,67,68] that with repeated smoking in the course of a day, there would be a gradual buildup of carboxyhemoglobin. This theory is based on analysis of alveolar air[64-71] carbon monoxide as well as several assumptions which have not been supported by actual blood analysis by Castleden and Cole.[62]

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The above observations support the theory that smokers fix a level of carboxyhemoglobin saturation that is not exceeded in the course of a day. Reducing the carbon monoxide content of cigarette smoke might mean that a given individual could then smoke more without violating his personally-set level.

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b. Dose-response relationships. There is no consistent relationship between the amount of cigarettes consumed and carboxyhemoglobin levels. An examination of the range of values indicates that there is a considerable amount of overlapping. For instance, Balbo et al.[72] reported the following results derived from Parisian volunteers.

Amount cig. (no. subjects)	Mean	Range
nonsmokers (44)	1.9	0-7
5 cigarettes daily (34)	2.1	0-9
10 cigarettes daily (32)	2.2	0-9.5
15 cigarettes daily (16)	2.2	0-5.9
20 cigarettes daily (20)	2.2	0-6.9
30 cigarettes daily (7)	2.8	0-5.2

The other reports do not show range of values for various groups of smokers.[73-75] The presence of a dose-response relationship is questionable unless the results are subjected to statistical analysis.

C. Practical Aspects of Carboxyhemoglobin Level

That carbon monoxide present in cigarette smoke is absorbed in the blood of smokers has prompted several investigators to suggest means of reducing the carbon monoxide emitted from cigarettes.[76-78] However, it should be noted that the amount absorbed by the smoker is to a large extent influenced by the manner of smoking. Robinson and Forbes[79] concluded that puff volume influences the delivery of carbon monoxide from cigarettes, just as does the porosity of the cigarette paper.

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Another suggestion has been to publicize the relative amount of carbon monoxide emitted from cigarettes, in the same manner as nicotine and tar contents are stated. The pros and cons have been discussed in correspondence published in Journals.[80-89] In addition to the factors that influence carboxyhemoglobin blood levels discussed in this chapter, there is an additional factor: the alteration of nicotine in the cigarette influences the consumption of cigarettes and, in turn, the carboxyhemoglobin level.[90-94] A change in the carbon monoxide content of cigarette smoke influences the smoking pattern and cigarette consumption of the individual, as though there is a self-regulating factor that keeps carboxyhemoglobin at a level that is constant for a particular smoker. More investigation is needed to determine the factors responsible for a relative fixation of carboxyhemoglobin levels in smokers. The fundamental issue thus far resolved is the health consequence of increasing or reducing the carbon monoxide in cigarette smoke. This question is answered in the next two chapters.

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